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Ciprofloxacin treatment of chlamydial infections of urogenital tracts of women

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SUMMARY Ciprofloxacin was evaluated in chlamydial infections of the urogenital tracts of women treated with a dosage regimen of 500 mg orally twice a day for seven days. Of the 40 women evaluated, 30 were infected with *Chlamydia trachomatis* only, two were infected with *Neisseria gonorrhoeae* only, and a further eight had combined gonococcal and chlamydial infections. Ten were found to be harbouring *Chlamydia trachomatis* in the urethra as well as the cervix. *Neisseria gonorrhoeae* was eradicated from all patients with or without concomitant chlamydial infection. The overall chlamydial reisolation rates were 14% (5/35) four weeks after treatment and 23% (6/26) 11 weeks after treatment. The organism was not reisolated from the urethra of any of the patients after treatment. Ciprofloxacin was effective against *Mycoplasma hominis*, but almost completely ineffective against *Ureaplasma urealyticum*.

The yearly statistical returns from the Department of Health and Social Security for 1983 show that in women attending sexually transmitted disease (STD) clinics in England 36 406 new cases of non-specific genital infection (NSGI) and 17 929 cases of gonorrhoea were diagnosed. This is probably an underestimate of the true incidence, as 97 673 new cases of non-gonococcal urethritis (NGU) and 30 464 cases of gonorrhoea were diagnosed in men in the same year.[1] Chlamydial infections of the cervix are responsible for many of the conditions recorded as NSGI, and *Chlamydia trachomatis* is also present in up to half the women with gonorrhoea.[2,3] The widely practised treatment of gonococcal infections with single doses or short courses of penicillin or alternatives that have no effect on *C trachomatis* therefore needs re-evaluation, as patients with combined gonococcal and chlamydial infections are at a high risk of persistent chlamydial infection and its associated complications.[4]

Until recently, tetracycline was the only drug that was effective against both gonococcal and chlamydial infections. Unacceptably high failure rates have been found in patients with gonorrhoea, however, especially women,[4] and both chromosomal and plasmid encoded resistance to tetracycline in *Neisseria gonorrhoeae* have significantly reduced the efficacy of the drug.[5]

Ciprofloxacin is a quinolone with high in vitro activity against *N gonorrhoeae*, including β lactamase producing strains. It has a low (0·01 mg/l) minimum inhibitory concentration (MIC),[6] and resistance does not readily develop after serial subculture of bacteria in media containing this agent. It is also effective in vitro against *C trachomatis*,[6,7] *Ureaplasma urealyticum*, and *Mycoplasma hominis*[8] in concentrations that are higher than those effective against *N gonorrhoeae* but still within attainable peak serum concentrations.

We evaluated the efficacy of ciprofloxacin 500 mg twice daily for seven days in men with uncomplicated gonococcal, chlamydial, and non-gonococcal non-chlamydial urethritis.[9] We concluded that the drug cured gonorrhoea, but was only partly effective against *U urealyticum*, and almost completely ineffective against *C trachomatis* in the doses given. In the present study we assessed the efficacy of ciprofloxacin in women with chlamydial or gonococcal, or combined infections of the cervix or the urethra, or both, using the same formulation and dosage regimen as previously used in our study in men.[9] We also observed the effect of ciprofloxacin on genital mycoplasmas in these patients.

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Patients and methods

New women patients seen at this hospital with a laboratory confirmed diagnosis of chlamydial, gonococcal, or combined infection of the cervix, urethra, or both, were included in the study if they were over 18 years old, had not received an antimicrobial agent in the preceding month, had no history of allergy to quinolones, and gave informed consent. We excluded women who were pregnant or who were of childbearing age but not taking oral contraceptives or fitted with an intrauterine contraceptive device. The study was approved by the local ethical committee.

HISTORY, EXAMINATION, AND LABORATORY INVESTIGATIONS

Symptoms and signs, demographic data, past history, and history of recent exposure were recorded.

Urethral specimens were collected using sterile cotton tipped ENT swabs (Medical Wire and Equipment Co, Corsham, Wiltshire) for smears for Gram staining and were also inoculated directly on to modified Thayer-Martin medium for culture of *N gonorrhoeae*. A similar swab was also taken for culture of *C trachomatis* at the second visit (before treatment) from any patient who had yielded the organism from the cervix.

The appearance of the cervix was noted, and swabs were taken from the endocervix for Gram staining and for culture for *N gonorrhoeae, C trachomatis,* and mycoplasmas. Vaginal secretions were also cultured for *Trichomonas vaginalis* and yeasts.

Gonorrhoea was diagnosed if Gram stained urethral or cervical smears showed Gram negative intracellular diplococci, and was subsequently confirmed by culture. Isolation of *C trachomatis, U urealyticum,* and *M hominis* was by methods described previously.[9] We measured MICs of ciprofloxacin against *N gonorrhoeae* and *C trachomatis* as described previously, and MICs against mycoplasmas as described by Taylor-Robinson and Furr in microtitre plates using a standardised inoculum of 10^3 to 10^4 colour changing units (ccu)/ml.[10]

Blood was taken initially and seven days later for full blood counts and biochemical profiles. Serological tests for syphilis were also performed.

TREATMENT

Each patient was given a seven days' supply of ciprofloxacin 500 mg, to be taken twice a day by mouth. Patients were advised to abstain from sexual intercourse until they and their partners were cured of infection, and to ask their consorts to attend our clinics for men. Contact slips were issued, and all patients with gonorrhoea were interviewed by our contact tracers.

FOLLOW UP

The patients were asked to return upon completion of treatment and subsequently at 1, 4, and 11 weeks after treatment (or at any time in the event of any new development). At each visit, the patients were asked about interim medication, symptoms, and further sexual exposure. If this had been with the same partner, they were asked whether or not he had been treated before sexual intercourse was resumed.

Swabs were taken from the urethra and cervix for culture of *N gonorrhoeae* and *C trachomatis* on the first two follow up visits, but only for *C trachomatis* on subsequent visits. Specimens were also taken for culture of mycoplasmas on every follow up visit from patients who had yielded the organisms before treatment.

If *N gonorrhoeae* or *C trachomatis* was isolated again, treatment was deemed to have failed unless the patient had resumed sexual intercourse with the same partner before he had completed his treatment or with a new partner, which suggested reinfection.

Results

Of 40 patients enrolled in the study, three attended for follow up only one week after treatment and a further four attended only one and four weeks after treatment.

STATUS BEFORE TREATMENT

Chlamydial infection of the cervix was found in 38 women, eight of whom had concurrent gonorrhoea; the other two patients had gonorrhoea only. Urethral swabs were taken from 28 of the 38 patients with chlamydial cervicitis, and 10 (36%) were found to be positive. *U urealyticum* was isolated from 37 (93%) and *M hominis* from 15 (38%). All patients from whom *M hominis* was isolated also yielded *U urealyticum.*

The MICs of ciprofloxacin were 1–2 mg/l for the *C trachomatis* strains isolated, less than 0·01 mg/l for gonococcal isolates, 0·5–2 mg/l for *U urealyticum*, and 0·25–0·5 mg/l for *M hominis.*

SEXUAL PARTNERS

The consorts of 37 women attended our male clinics; 24 had NGU, and 10 had gonorrhoea, nine of whom developed post-gonococcal urethritis. No evidence of urethritis was found in three men. None of the male consorts was tested for *C trachomatis*, but all those with evidence of urethritis were treated with oxytetracycline.

OUTCOME OF TREATMENT

Chlamydial infection of the cervix

The organism was isolated from the cervix again four

Table 1 *Follow up of 38 patients with chlamydial infection of the cervix*

Week after treatment	*No seen*	*No attending only up to specified week*	*Results after treatment*		*Further intercourse:*			
			Negative	*Positive*	*None*	*With same partner*		*With new partner*
						Untreated	*Treated*	
1	38		38	0	38			
		3	3	0	3			
4	35		30		12	0	15	3
				5*	0	1	2	2
		4	4	0	1		1	2
11	26		25		8	0	15	2
				1	1			

*Five patients positive at week 4 were withdrawn from trial.

weeks after treatment in five patients and 11 weeks after treatment in one patient. Five of these six patients had resumed sexual intercourse, three with a new or untreated consort (table 1).

Chlamydial infection of the urethra

Of the 10 patients from whose urethras *C trachomatis* was isolated, one did not return for follow up, two attended only one week, three attended only one and four weeks, and a further three attended 1, 4, and 11 weeks after treatment. The organism was not isolated again from the urethra of any of the patients followed up. In one patient, however, *C trachomatis* was isolated again from the cervix four weeks after treatment (table 2).

N gonorrhoeae

Eight of the 10 patients from whom *N gonorrhoeae* was isolated were treated with ciprofloxacin, and all had negative cultures on two successive follow up visits. Gonorrhoeae was also cured in two patients who were treated with procaine penicillin, but as both had concurrent chlamydial infection they were admitted to the trial and received ciprofloxacin.

Mycoplasmas

Of the seven patients from whom *M hominis* was isolated again at follow up (table 3), six had resumed sexual intercourse, two with a new partner and four with the same partner who had been treated with a different antibiotic.

SIDE EFFECTS

None of the patients complained of any untoward side effects. On direct questioning, four had experienced possible side effects, which were all mild and included nausea and mild abdominal discomfort. Haematological and biochemical screening did not show any abnormalities.

Discussion

The optimum follow up period to confirm cure or detect failure for a particular treatment regimen in treating chlamydial infections is unknown, because recurrence of the infection may not be detected until several weeks after treatment.[9 11] It is always difficult to distinguish relapse from reinfection when evaluating the outcome of treatments of an STD, but bias resulting from inaccurate sexual histories can be minimised by cross checking with the case sheets of sexual partners, as was attempted in this study.

The reisolation rates of *C trachomatis* from the cervix were 14% (5/35) of women seen four weeks and 4% (1/26) of those seen 11 weeks after treatment. After exclusion of those thought to have been reinfected, the

Table 2 *Follow up of nine patients with chlamydial infection of urethra concurrently with cervical infection (results included in table 1)*

Week after treatment	*No seen*	*No attending only up to specified week*	*Results after treatment*		*Further intercourse:*			
			Negative	*Positive*	*None*	*With same partner*		*With new partner*
						Untreated	*Treated*	
1	9		9	0	9			
		2	2	0	2			
4	7		7*	0	3	1	1	2
		3	3	0	2			1
11	3		3	0	2		1	

**Chlamydia trachomatis* isolated from cervix in one patient, who was then withdrawn from trial.

Table 3 *Effect of ciprofloxacin on mycoplasmas (Mycoplasma hominis and Ureaplasma urealyticum) in 40 women*

	No (%) positive/No tested for:	
	M hominis	*U urealyticum*
At presentation	15/40 (38)	37/40 (93)
Follow up after:		
1 Week	1/12 (8)	22/25 (88)
4 Weeks	2/10 (20)	21/23 (91)
11 Weeks	4/9 (44)	18/19 (95)

failure rate was 6% (2/35) at four weeks and remained 4% at 11 weeks after treatment. These treatment failure rates are comparable with those reported by the same observers for a seven day course of oxytetracycline in the treatment of chlamydial infections of the cervix—that is, at four weeks after treatment 7% (17/220) overall and 6% (12/220) after excluding women thought to have been reinfected.[11]

Ten patients had chlamydial infection of the urethra as well as cervical infection before treatment. The organism was not isolated again from the urethra of any of the seven patients tested four weeks after treatment, although in one patient the organism was isolated again from the cervix. This was in sharp contrast to our finding of reisolation in 79% (11/14) of men with chlamydial urethritis four weeks after treatment with the same dose of ciprofloxacin.[9] The reasons for this difference between the sexes may lie either in the anatomical site or degree of infection, or in pharmacokinetic differences between the sexes regarding ciprofloxacin.

Infection of men may involve the glands of Littré or the posterior urethra, or even the prostate, which are not relevant to women and may be more refractory to access by ciprofloxacin. The degree of urethral infection as judged by counting chlamydial inclusions obtained by swabs in our clinics is usually about 1–10 inclusion forming units (ifu)/culture in women, but 10–>1000 in men. The MIC for chlamydial strains from men in our previous study[9] was no higher than those obtained from women in the present study, which would not be expected as both groups were drawn from the same clinic population.

As far as differences in pharmacokinetics are concerned, the ciprofloxacin formulation and dose used in women was the same as in the men—indeed 15 of the women were treated at the same time as our trial in men and with the same batch of ciprofloxacin.[9] It is possible that the actual tissue drug concentrations attained from a given dose were higher in women than in men because of different mean body weights. This has been observed with other chemotherapeutic agents, and has produced similarly better results of treating chlamydial infections in non-pregnant women than in men.[12,13] The MIC of ciprofloxacin for *C trachomatis* is high in relation to maximum achievable blood concentrations. Differences in therapeutic efficiency between the sexes could thus be greater than has been seen with drugs such as erythromycin, which has a greater margin between MIC and peak blood concentration.

We conclude that ciprofloxacin 500 mg twice a day for seven days cures gonorrhoea. Indeed, excellent cure rates have been reported after single doses of 100–250 mg.[14] Ciprofloxacin is partially effective against *C trachomatis*. Although failure rates against *C trachomatis* infections in women are comparable with those we found with a seven day course of oxytetracycline,[11] further studies are necessary to see whether better cure rates can be achieved using a higher dose or longer course of treatment, or both. Ciprofloxacin was also effective against *M hominis*, but almost completely ineffective against *U urealyticum*.

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